The Effect of Topical Indomethacin and Topical Corticosteroid on UVB Induced Erythema

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**Background:** Indomethacin is a potent inhibitor of prostaglandins biosynthesis. Sunburn erythema is mainly mediated by prostaglandins.

**Objective:** Our purpose was to compare objectively the effectiveness of topical indomethacin with topical corticosteroid on the suppression of UVB erythema.

**Methods:** Sixteen male medical students who had not exposed their back skin during the last year were included in this study. According to the individual's MED 1, 2, and 3 MED of UVB were irradiated on each back in triplicate lines. Immediately after UVB irradiation, 2.5% indomethacin solution and 0.25% desoximethasone were applied to each row with one row left for control. 24 hours after the initial application the intensity of each erythema was measured by the naked eye and by colorimeter.

**Results:** The suppressive effectiveness of 2.5% indomethacin solution on UVB induced erythema was superior to that of 0.25% desoximethasone. The L* and a* value of colorimeter were significantly correlated to the differences of UVB induced erythema among the experimental and control groups is a useful and rapid method to evaluate the UVB induced erythema, and can give a numerical expression to eye perception.

**Conclusion:** Our data confirm that topical indomethacin has a stronger suggestive effect on UVB erythema than that of topical corticosteroid. We suggest that the suppressive effect of indomethacin is mainly due to the inhibition of prostaglandins biosynthesis. The colorimeter CR-200(MINOLTA) is well correlated with the naked eye score and is a useful instrument for objective measurement of the degree of erythema.

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The cyclo-oxygenase products of arachidonic acid metabolism have been implicated in the inflammatory response to ultraviolet radiation(UVR)\(^1\). The topical indomethacin has been known to reduce the intensity of sunlight induced erythema. There have been many reports describing the integral role of prostaglandins in mediating UVR-induced redness\(^1\). Prostaglandins, largely of the E series, are known mediators of UVB-damaged skin\(^1\). Black et al\(^2\) showed that the concentration of PGE\(_2\) in suction blister fluid following UVB irradiation was increased at 2 hours, reached a maximal at 24 hours and fallen to control levels by 48 hours.

Although corticosteroids are the most potent of known anti-inflammatory agents, their suppressive effect against UV erythema are modest. Ljunggren and Moller\(^3\) found that alcoholic solutions of hydrocortisone and betamethasone valerate applied before irradiation were efficacious in inhibiting the erythema from 1 and 1.5 MED of UVB. Burdick\(^4\) et al reported that doses in excess of 1 MED were inadequate for differentiating the various topical steroid preparations in the assay of UV induced erythema suppression. The influence of topical steroid on UV erythema is less clear.

The main purpose of this study was to evaluate and compare objectively the suppressive effect of topical indomethacin and desoximethasone on UVB induced erythema.
was 285-350nm, with a peak at 310-315nm. The intensity of the radiation at the skin surface was measured by Waldmann’s UV-meter every experimental day.

According to their individual MED, the right back of each subject was irradiated in triplicate with the dose of 1, 2, and 3 MED.

The central row of the irradiated area was applied with an alcoholic base solution only as control and 2.5% indomethacin and 0.25% desoximetasone solution were applied to both sides of triplicated irradiated lines with occlusive}

Table 2. Comparison of erythema between the control, indomethacin treated and corticosteroid treated sites by naked eye score 24hrs after treatment

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Indomethacin Treated</th>
<th>Desoximetasone Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MED</td>
<td>2.0</td>
<td>1.1 ± 0.12</td>
<td>1.8 ± 0.20</td>
</tr>
<tr>
<td>2 MED</td>
<td>3.0</td>
<td>1.4 ± 0.34</td>
<td>2.6 ± 0.34</td>
</tr>
<tr>
<td>3 MED</td>
<td>4.0</td>
<td>2.1 ± 0.31</td>
<td>3.8 ± 0.27</td>
</tr>
</tbody>
</table>

0: no erythema
1: faint erythema
2: minimal erythema
3: more pronounced erythema
4: intense and deep erythema

Table 3. The L*, a* and b* values after application of indomethacin and desoximetasone compared with the control group

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Indomethacin</th>
<th>Desoximetasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MED</td>
<td>L*</td>
<td>61.59 ± 2.1</td>
<td>63.10 ± 2.3A</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>17.39 ± 2.2</td>
<td>14.07 ± 1.7B</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>18.55 ± 1.3</td>
<td>19.34 ± 1.7</td>
</tr>
<tr>
<td>2 MED</td>
<td>L*</td>
<td>59.57 ± 2.9</td>
<td>32.57 ± 2.9B</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>18.31 ± 1.9</td>
<td>14.31 ± 1.7B</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>17.49 ± 1.5</td>
<td>19.17 ± 1.3</td>
</tr>
<tr>
<td>3 MED</td>
<td>L*</td>
<td>58.49 ± 2.0</td>
<td>62.49 ± 3.1B</td>
</tr>
<tr>
<td></td>
<td>a*</td>
<td>19.86 ± 1.6</td>
<td>15.05 ± 2.1B</td>
</tr>
<tr>
<td></td>
<td>b*</td>
<td>16.62 ± 1.3</td>
<td>18.33 ± 1.4</td>
</tr>
</tbody>
</table>

A<sub>p</sub> < 0.05, compared with control values
B<sub>p</sub> < 0.01, compared with control values

MATERIALS AND METHODS

Sixteen male medical students who had not exposed their back skin during the last year were included in this study.

The light source was an array of 10 fluorescent sunlamps 20W/12 (PHILIPS) set in Waltermann 800. The spectral irradiance of the UVB source dressing technique for 6 hours. After 24 hours of the initial application, the intensity of erythema was graded by naked eye and by the colorimeter CR-200(MINOLTA).

The intensity of erythema was graded clinically as follows: 0, no erythema; 1, faint erythema; 2, minimal erythema; 3, more pronounced erythema; 4, intense and deep erythema.
Table 4. Color difference (ΔE) in 2.5% indomethacin treated and 0.25% desoximethasone treated sites compared with the control group

<table>
<thead>
<tr>
<th></th>
<th>2.5% indomethacin treated</th>
<th>0.25% desoximethasone treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N.B.S. unit</td>
<td>Difference in Visual sensation</td>
</tr>
<tr>
<td>1 MED</td>
<td>3.73 ± 2.5</td>
<td>Appreciable</td>
</tr>
<tr>
<td>2 MED</td>
<td>5.27 ± 2.2</td>
<td>Appreciable</td>
</tr>
<tr>
<td>3 MED</td>
<td>6.48 ± 1.6</td>
<td>Much</td>
</tr>
</tbody>
</table>

\[ \Delta E = (\Delta L^2 + \Delta a^2 + \Delta b^2)^{1/2} \]
N.B.S. unit : National Bureau of Standard unit

As the assessment of erythema, we also measured the skin color using a colorimeter CR-200 (MINOLTA), which measures chromatically as L*(represent degree of lightness), a*(represent degree of redness), b*(represent degree of yellowness) value by silicon photocells. This rapid method can give numerical expression to eye perception. The measuring head contains a pulsed xenon-arc lamp to illuminate the sample and 6 silicon photocells. Three of the photocells monitor the output of the lamp; the other 3 measure the light reflected from the sample. The apparatus offers 5 different color systems for measuring absolute chromaticity. We used the system L*a*b*. The L*, a*, b* values could give color image and color difference (ΔE) by color difference formula (Table 1). The colorimeter was calibrated by white ceramic standard board every experimental day.

RESULTS

In this study, the suppression effect of UVB erythema in 2.5% topical indomethacin was found to be significantly higher than that of 0.25% desoximethasone by the naked eye and by chromameter CR-200.

Figure 1 shows the degree of erythema of indomethacin and desoximethasone treated sites compared with the control. Table 2 gives the values of the degree of erythema by naked eye score among 3 groups. The sites of 2.5% indomethacin application gave marked suppressed erythema at 1, 2, and 3 MED all. But only mild suppression was observed on the 0.25% indomethacin application site, increasing trend of L*(lightness) was evident compared to that of the control group and the a* value decreased at all MED sites as compared with the control value and statistical analysis, using t-test, showed significant differences between control and 2.5% indomethacin treated group in L* and a* value. In the 0.25% desoximethasone applied sites, the calculated colorimeter data expressed a difference at 1 MED and there were no differences statistically at 2 and 3 MED in L* and a* values (Table 3). There were no statistical differences in 1 and 3 MED compared with the control and desoximethasone treated group.

As were depicted in Figure 2 and 3, the L*(lightness) value was significantly increased on 2.5% indomethacin applied site compared with the control or desoximethasone treated group. Figure 3 shows that the scores of a*(redness) are highly decreased on the 2.5% indomethacin applied site compared with the control or desoximethasone treated group.

Using the National Bureau of Standard unit schemes, the difference in visual sensation was evaluated.

The color differences (ΔE) between indomethacin in treated groups and control sites were 3.73 ± 2.5, 5.27 ± 2.2 and 6.48 ± 1.6 N.B.S. unit respectively at 1, 2, and 3 MED but those between 0.25% desoximethasone treated group and control were 2.64 ± 2.2, 0.62 ± 2.3 and 0.76 ± 1.8 at 1, 2, and 3 MED (Table 4).

DISCUSSION

Erythema induced by ultraviolet irradiation has been shown to be mediated by prostaglandins. In a study of human sunburn reaction, it has been demonstrated that PGE levels were elevated before the onset of erythema. At 24hrs, when maximal clinical erythema was observed, the PGE levels reached 150% of the control value. The PGE plays an important role in the early phase of sunburn (0-24hr) where indomethacin is most effective. Indomethacin has been shown to inhibit the prostaglandin biosynthesis by the human skin.

It has been generally understood that the
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Fig. 1. The degree of erythema of control, indomethacin and desoximethasone treated sites after 24hrs of UVB irradiation (1, 2, and 3 MED). Left: 0.25% desoximethasone treated site, Center: Control, Right: 2.5% indomethacin treated site.

Fig. 2. The L* (lightness) value after topical application of 2.5% indomethacin and 0.25% desoximethasone compared with control.

Fig. 3. The a* (redness) values after topical application of 2.5% indomethacin and 0.25% desoximethasone compared with control.

The synthesis of prostaglandins is stimulated concomitant with the increase of inflammation to maximum level. Indomethacin is known to decrease the UVB induced erythema when applied topically in regular intervals after irradiation, probably via the inhibition of prostaglandin synthesis. There is mounting evidence that prostaglandins are likely candidates for mediating sunburn erythema, and a measurable increase in the amount of prostaglandins occurs in skin exposed to UVB. Gengi and Toru demonstrated that the organ culture system employed for determining the level of prostaglandin synthesis is reliable for evaluation of inflammation genesis due to UVA, UVB, UVC irradiation. In that experiment, LTC4, a 5-lipooxygenase metabolite, was not found to be associated with the development of UV-induced inflammation. Black et al. have recently reported that LTxB4 is not elevated in UVB-induced erythema, while there is a significant increase in 12-HETE, which is a 12-lipooxygenase product. LTB4 and LTC4 have been reported to increase vascular permeability when injected into the skin and in combination with PGE2, its activity arise synergistically.

Our study demonstrates that 2.5% solution of indomethacin indeed suppressed UVB induced erythema at all 1, 2 and 3 MED sites.

Although corticosteroids are the most potent, known anti-inflammatory agents, their suppressing effect against UV erythema is modest. Steroids may decrease the UV erythema by their well-known vasoconstrictor action on cutaneous vessels in a manner analogous to the blanching produced by the injection of epinephrine into UV-redden skin. It may be that the anti-inflammatory potency is not uniform but varies with the type of noxious stimulus and subsequent inflammatory reaction. It has been suggested in the past that steroid-induced vasoconstriction may be mediated by norepinephrine released. Weissman and Fell observed that the addition of hydrocortisone to fetal rat skin explant retarded and reduced cellular breakdown produced by UV-light.

The UV damage can be brought about by the rupture of lysosome with the release of hydrolytic enzymes. It is not fully clear how important lysosome labilization is in mediatory UV injury.
There are now numerous studies in the literature suggesting a lalient role for prostaglandins in mediating UVB-induced delayed erythema and only scant evidence indicating that corticosteroids have a significany inhibitory effect on the biochemistry of prostaglandins.

Until more is known of the detailed mechanism of prostaglandin biosynthesis the precise mechanism of inhibition of corticosteroid on prostaglandin biosynthesis is likely to remain speculative. On the other hand, since steroids probably stabilize lysosomes, after altering cell permeability, and have other anti-inflammatory properties, a suppressive effect on UVB-induced inflammation and the mechanism of steroid suppression of inflammation are incompletely understood, only experimental testing can be relied upon to predict the outcome of steroid use in the treatment of UVB burn and sunburn.

In our study, using a colorimeter, the suppression in 2.5% indomethacin compared to the control value was statistically significant at 1, 2, 3 MED (p<0.05). In addition, increased lightness (L*) and decreased redness (a*) was noted at 1, 2 and 3 MED and a remarkable finding was noted at 3 MED. On the other hand, 0.25% desoximethasone failed to produce any clear discrimination by naked eye and erythema could be noticeable only with 1 MED data calculated by using of the chroma meter CR-200 (MINOLTA). As can be concluded from these data, 2.5% topical application of indomethacin was superior to a potent topical corticosteroid application.

In our study, topical application of indomethacin and corticosteroid solution to ultraviolet light induced erythema expressed different results. However, measuring the erythema graded by visual comparison is subjective and gives inaccurate information. So, the effect of indomethacin and corticosteroids on UVB erythema was accessed objectively by using a Chroma Meter CR-200 (MINOLTA) and more objective erythema data between indomethacin treated and corticosteroid treated erythema were obtained. Our data are consistent with other data that indomethacin solution application immediately after irradiation suppresses the subsequent erythema against 1, 2 and 3 MED. Thus we can confirm the result of previous reports that topical application of an inhibitor of prostaglandins, indomethacin, to UVB-induced erythema suppresses the erythema and we agreed with Burdick et al that doses in excess of 1 MED are not sufficiently discriminating in topical corticosteroid effect on UVR induced erythema. So, based on this data, it is likely that corticosteroid cream has little or no quantifiable usefulness in altering cutaneous signs and symptoms during the early phase of sunburn. Consequently, the suppression effect of 2.5% indomethacin solution on UVB-induced erythema was superior to that of potent corticosteroid.

To conclude, this study has show that the measurement of UVB induced redness using Chroma Meter CR-200 is simple, fast, easily performed and it provides useful and objective data for comparing the UVB induced redness in various Conditions.

REFERENCES


